

The Enterohepatic Circulation with Key Transporter Proteins Mediating

Bile Acid Circulation

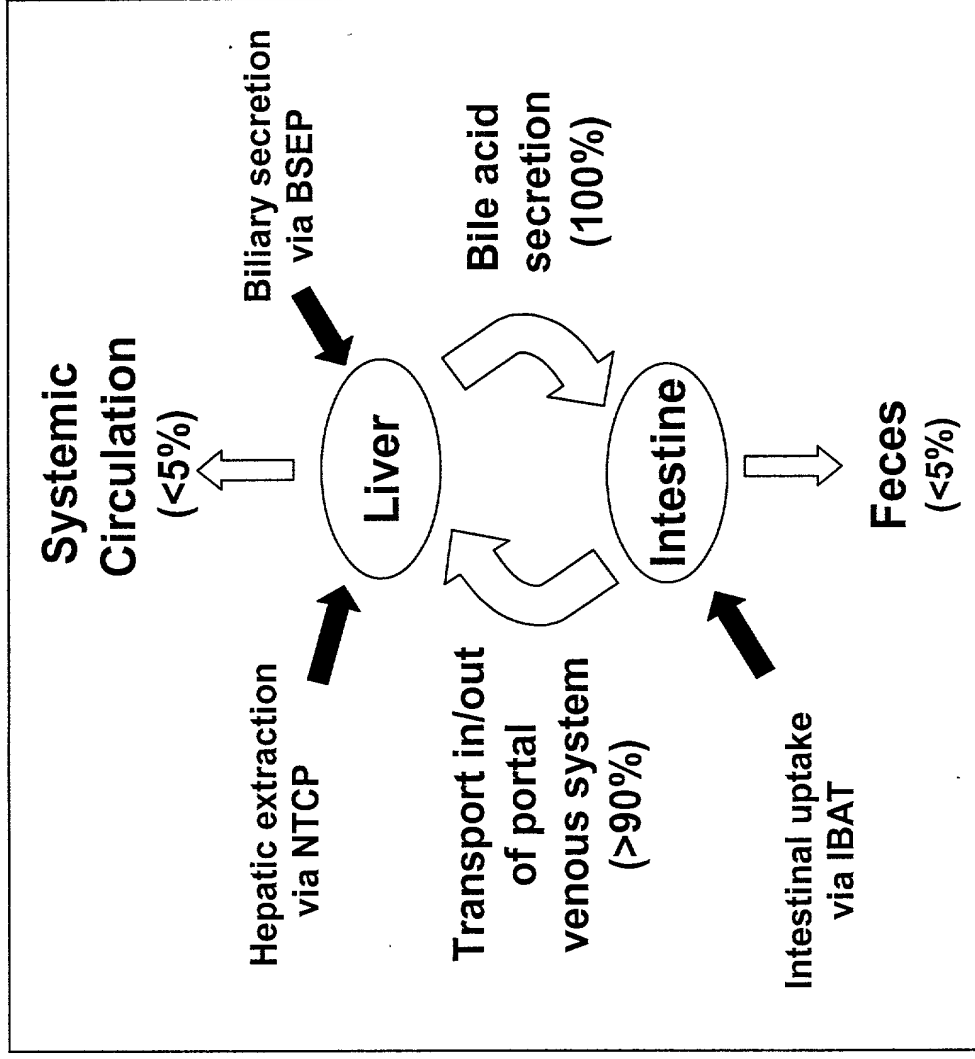
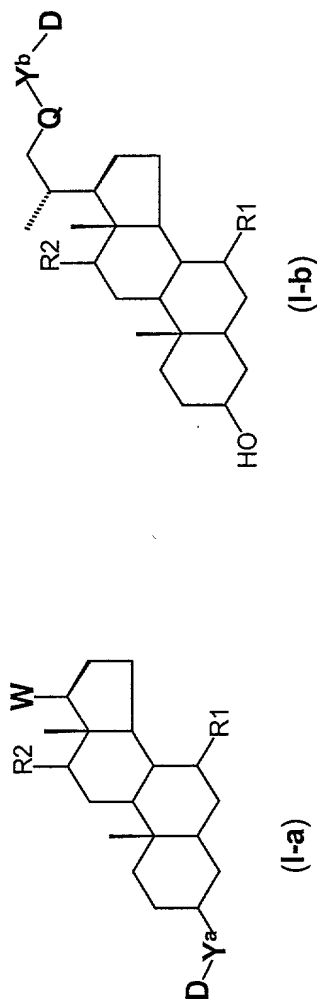


Figure 2

Bile Acid Prodrug Derivatives for Sustained Release of Drugs



Y^a , Y^b are cleavable linker groups

D is a drug moiety

Q is CH_2 or O

W is selected from the group consisting of $-CH(CH_3)W'$ where W' is a substituted alkyl group containing a moiety which is negatively charged at physiological pH, which moiety is selected from the group consisting of $-COOH$, $-SO_3H$, $-SO_2H$, $-P(O)(OR^6)(OH)$, $-OP(O)(OR^6)(OH)$, $-OSO_3H$ and pharmaceutically acceptable salts thereof

$R1 = R2 = \alpha-OH$ (from Cholate)

$R1 = \alpha-OH$, $R2 = H$ (from Chenodeoxycholate)

$R1 = \beta-OH$, $R2 = H$ (from Ursodeoxycholate)

$R1 = H$, $R2 = \alpha-OH$ (from Deoxycholate)

$R1 = \beta-OH$, $R2 = \alpha-OH$ (from Ursocholate)

$R1 = R2 = H$ (from Lithocholate)

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Hydroxyl or 1° and 2° Amine-Containing Drugs



Carboxylic Acid-Containing Drugs

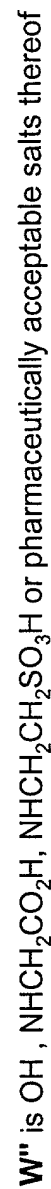
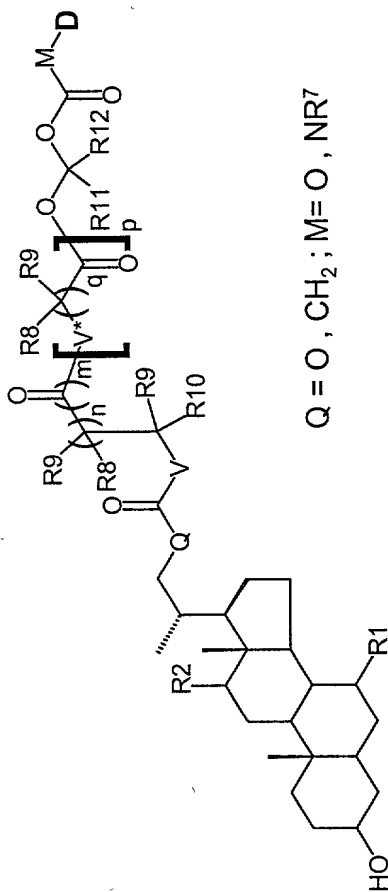
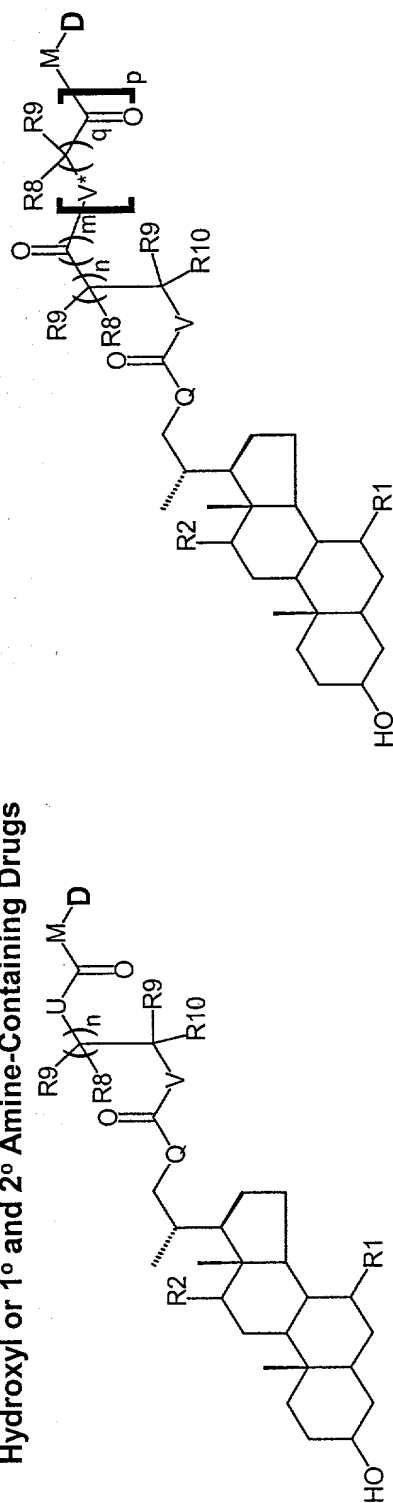


Figure 4- Generic Structures of Preferred Bile Acid C-24 Derivatives

Hydroxyl or 1° and 2° Amine-Containing Drugs



Q = O, CH₂; M = O, NR⁷

Carboxylic Acid-Containing Drugs

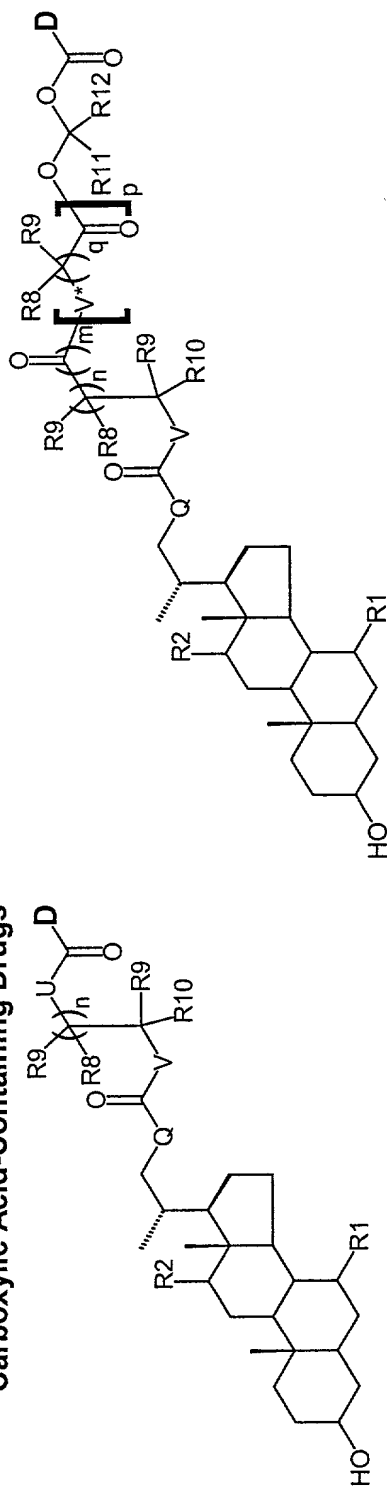


Figure 5 GABA Analog Derivatives and L-Dopa Derivatives



Generalized GABA Analog

Optionally Protected L-Dopa Analog

R14, R15, R16, R19 and R20 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl and substituted heteroarylalkyl;

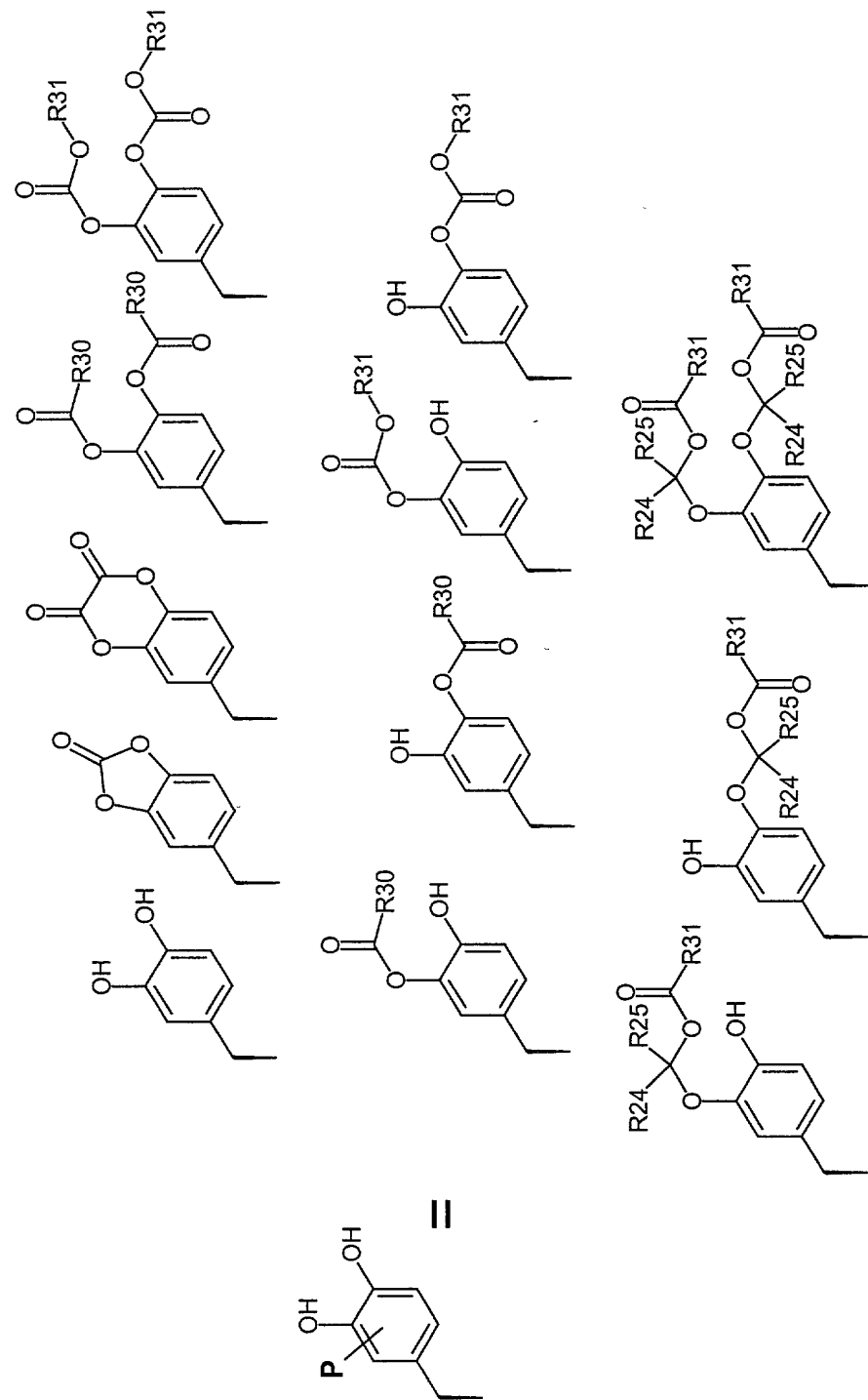
R17 and R18 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl and substituted heteroarylalkyl or optionally, R17 and R18 together with the carbon atom to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycloalkyl or bridged cycloalkyl ring;

P is a catechol protecting group (see Figure 6)

The GABA analog or L-Dopa analog is attached to the steroid nucleus in (I-a) or (I-b) either by replacement of one of the amino hydrogen atoms, or a hydrogen atom from one of the hydroxy groups of the catechol, or the hydroxyl group of the carboxyl moiety by a covalent bond to Y^a or Y^b


Figure 6:

Catechol Protection Strategies Applicable for L-Dopa Bile Acid Conjugates



R30 = hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl
 R31 = alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl
 R24, R25 = hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl
 or R24 and R25 together with the carbon to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycloalkyl or substituted heterocycloalkyl ring

(XII)



 (XIII)

Chemical structure (XIV) is a fluorene derivative. It features a fluorene core with a carboxylic acid group (-COOH) at position 2, a ketone group (=O) at position 9, and a polymer chain at position 1. The polymer chain is represented by a repeating unit in brackets with a subscript n , containing a drug moiety (M-DRUG) linked via an ester bond. Substituents R26 and R27 are shown at positions 6 and 7, respectively.

Chemical structure (XV) is a fluorene derivative. It features a fluorene core with a carboxylic acid group (-CH₂COOH) at position 9, a ketone bridge (=O) at position 10, and a polymer chain at position 2. The polymer chain is represented by a repeating unit in brackets with a subscript 'n'. The repeating unit consists of a carbon atom bonded to R23 and R22, and an oxygen atom bonded to an M-DRUG group. The label (XV) is positioned to the right of the structure.

M = O, NR7, CR8R9

L = CR8, N

m' is 0 to 6 ; n' is 0 to 6

 $K = 0, NR7, CR8R9; S(O)_j, j = 0, 1, \text{ or } 2$

Each of R21 to R23 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, substituted acyl, acylamino, substituted acylamino, alkylsulfinyl, substituted alkylsulfinyl, alkylsulfonyl, substituted alkylsulfonyl, alkylthio, substituted alkylthio, alkoxycarbonyl, substituted alkythio, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxy, substituted aryloxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroalkyloxy, substituted heteroalkyloxy, heteroaryloxy and substituted heteroaryloxy

Preferably R22 and R23 are independently selected from the group consisting of hydrogen, alkyl and substituted alkyl

R26 and R27 are independently selected from the group consisting of halo and lower alkyl (including branched alkyl)

Figure 8.24.53

Enterohepatic Circulation Mediated by Intestinal Peptide and Hepatic Anion Transporters

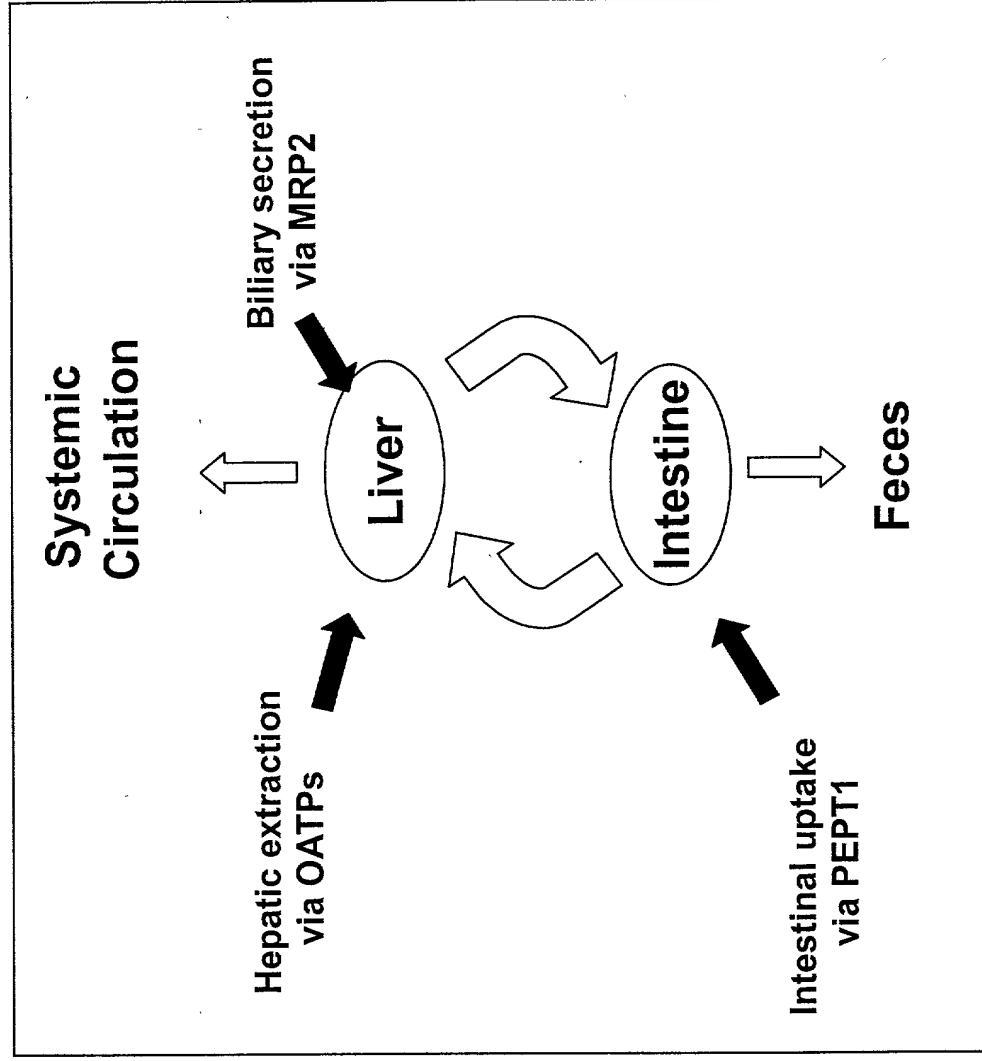


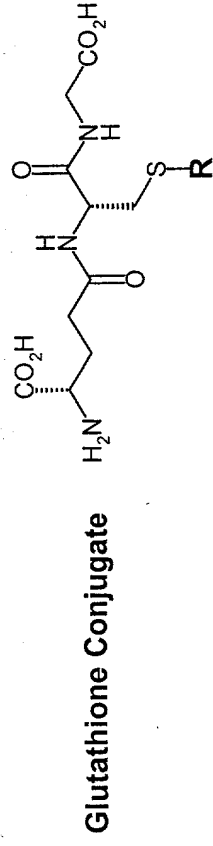
Figure 9

Enterohepatic Recirculating Prodrugs Based On Glutathione Mimetics

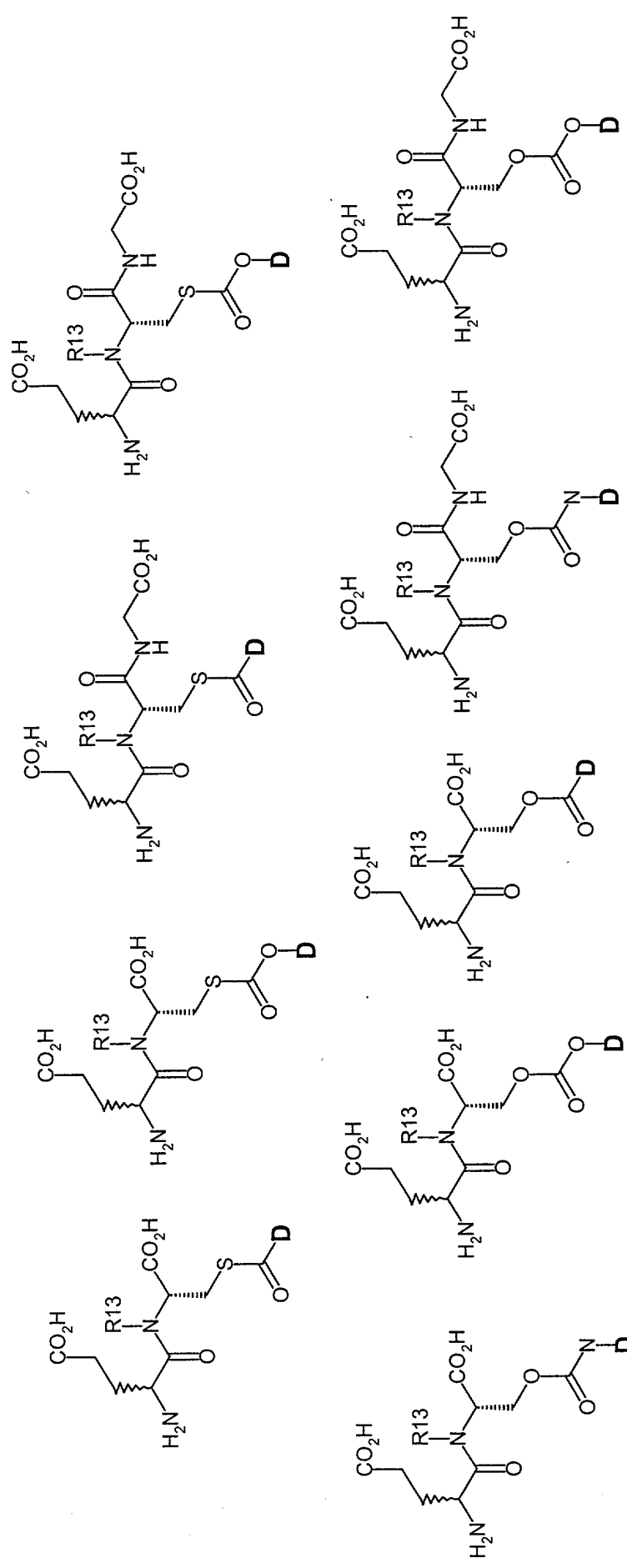
Substrate for OATP on sinusoidal membrane of liver

Substrate for MPR2 on canicular membrane of liver

Not transported by PEPT1



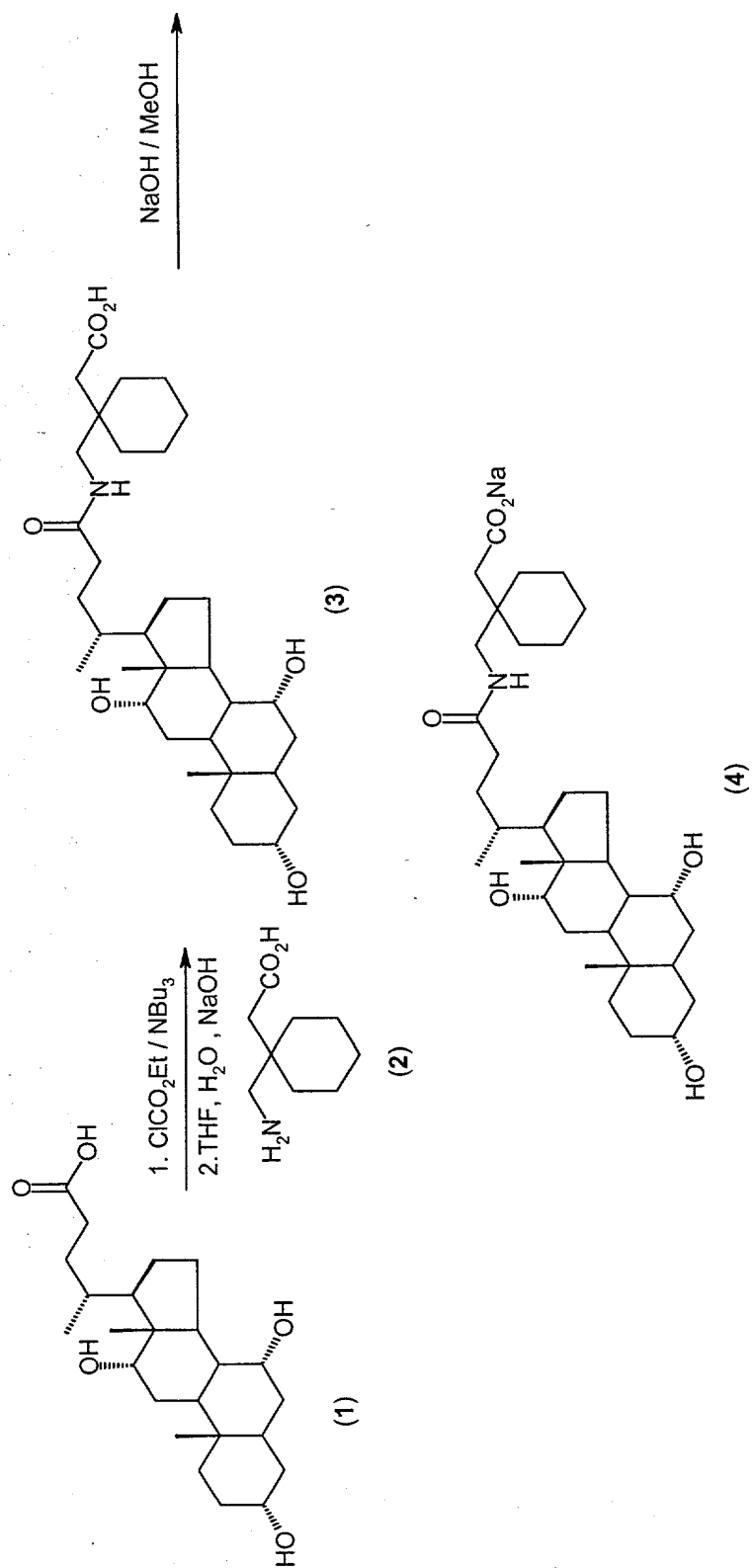
Examples of Di- and Tripeptide Prodrugs of Hydroxyl, Amine and Carboxylic Acid-Containing Drugs Based on Glutathione-Like Motif



R13 = H , lower alkyl

Use PEPT1 substrate with metabolically stable di- or tripeptide backbone to achieve intestinal absorption

Figure 10



Year	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100
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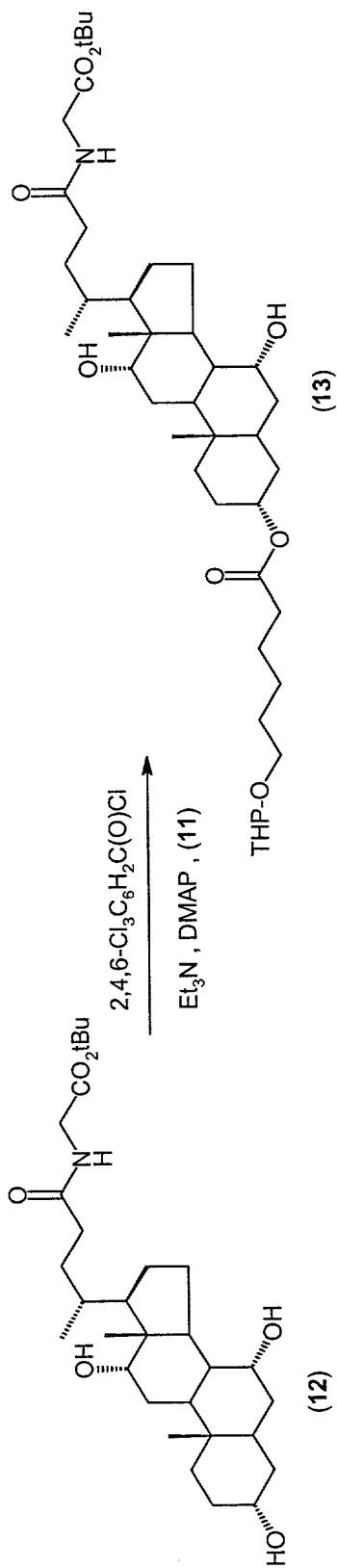


Figure 13

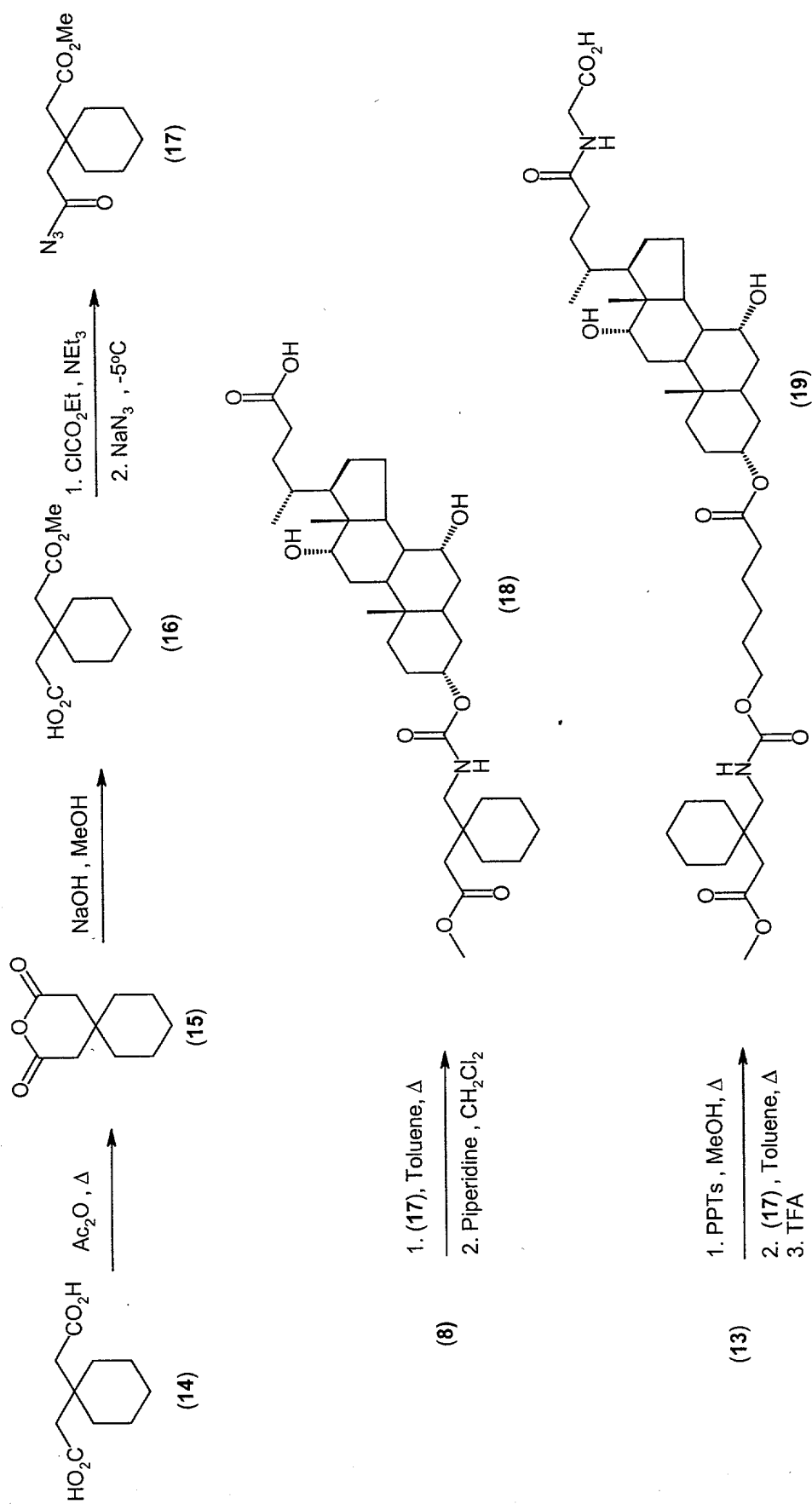


Figure 14 - Synthesis of Cholesteryl-Dopa Conjugates

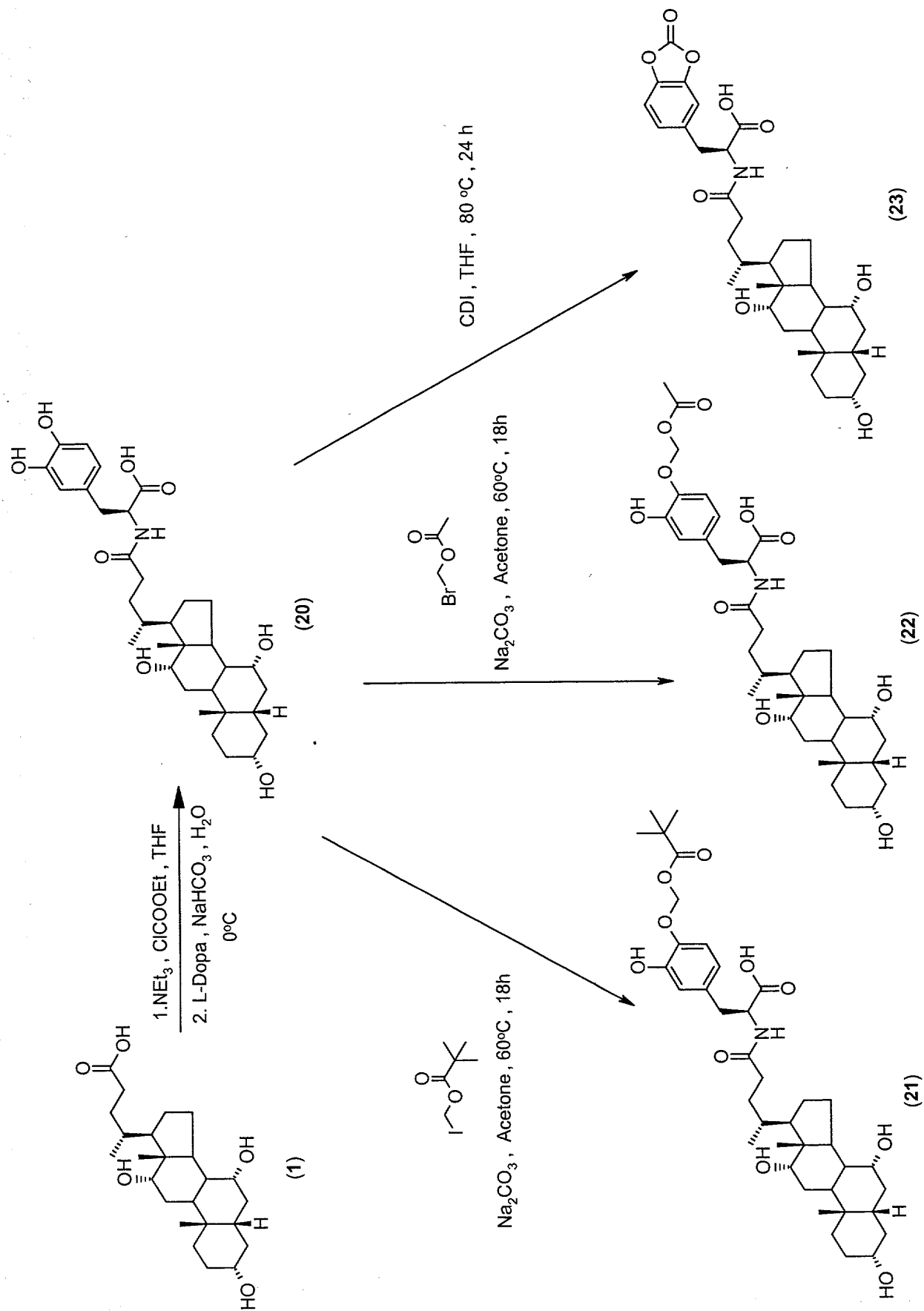
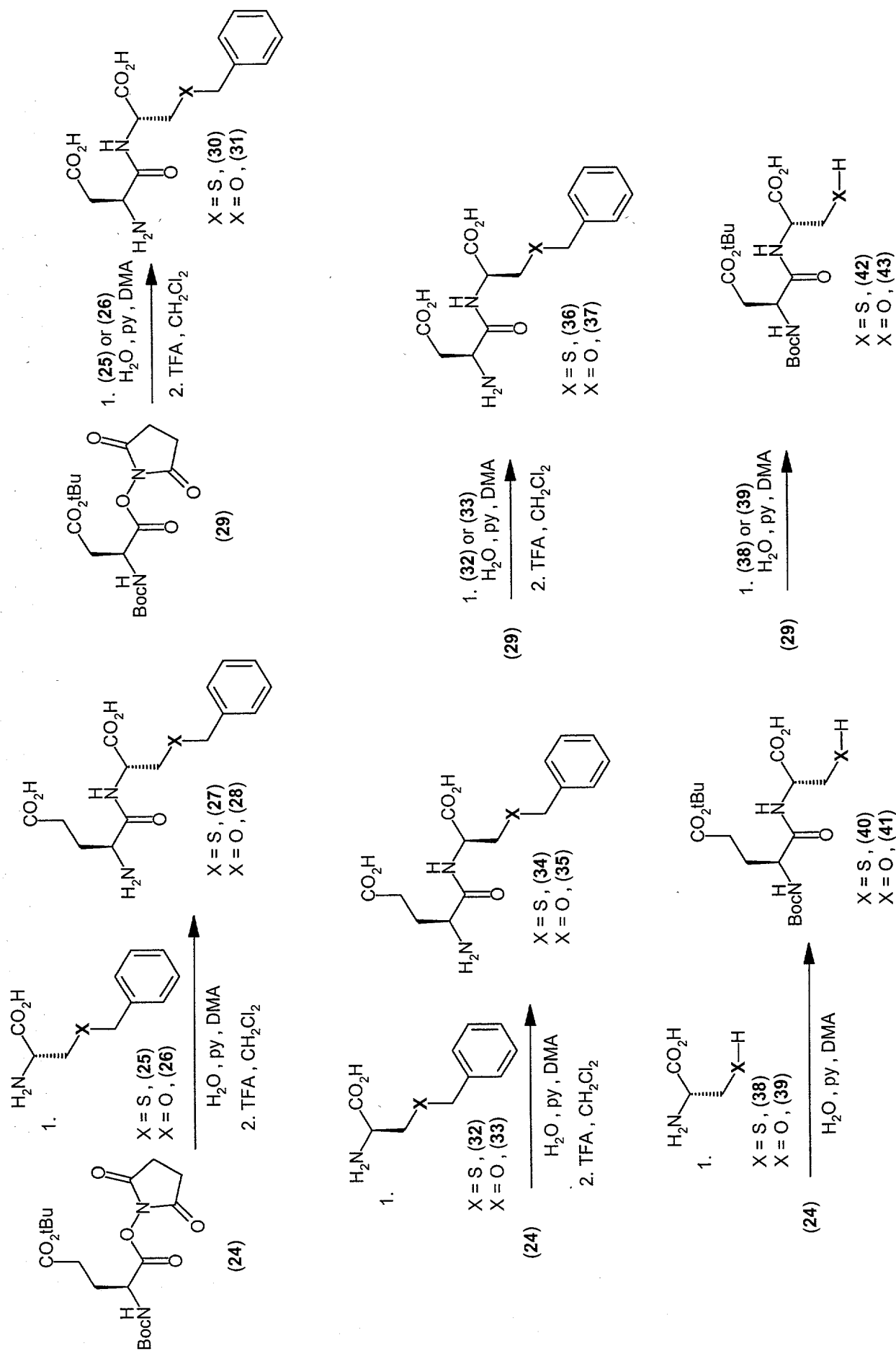


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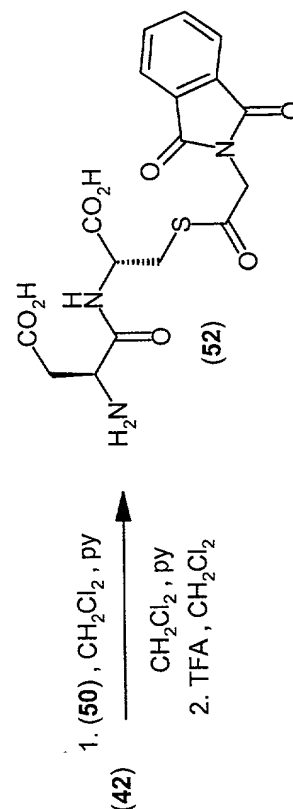
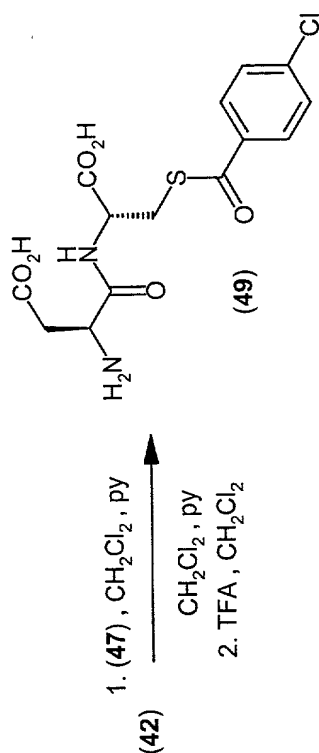
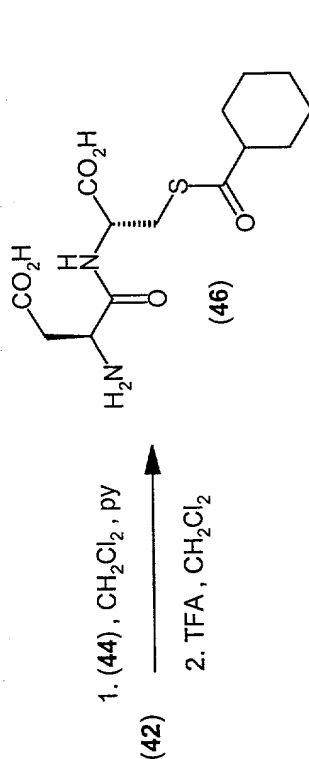
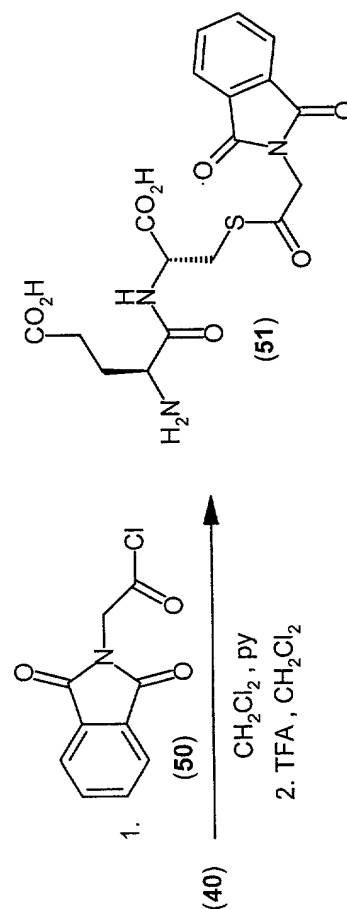
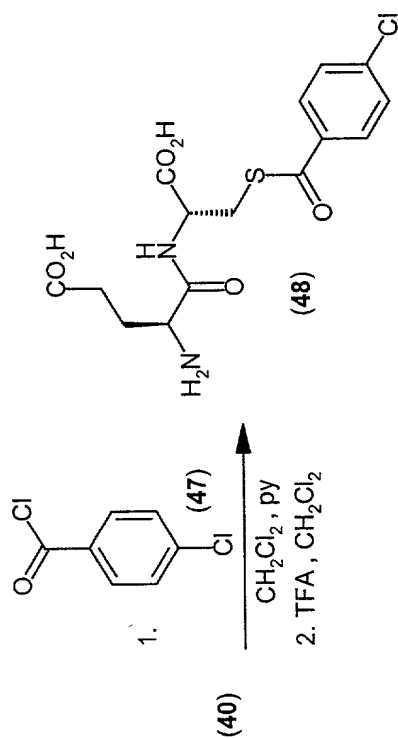
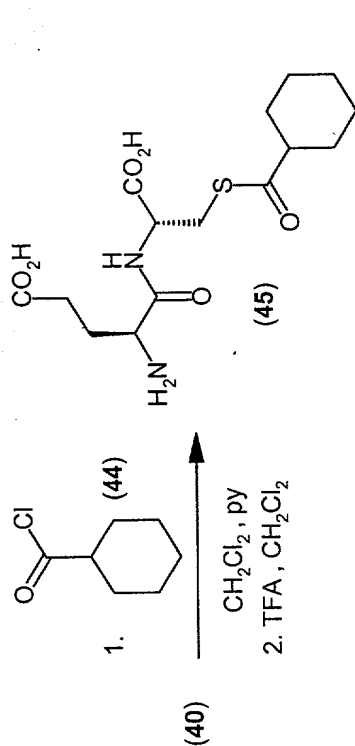


Figure 17

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